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Physical activity for strengthening fracture prone regions of the proximal femur

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Abstract

Purpose of review—Physical activity improves proximal femoral bone health; however, it remains unclear whether changes translate into a reduction in fracture risk. To enhance any fracture-protective effects of physical activity, fracture prone regions within the proximal femur need to be targeted.

Recent findings—The proximal femur is designed to withstand forces in the weight bearing direction, but less so forces associated with falls in a sideways direction. Sideways falls heighten femoral neck fracture risk by loading the relatively weak superolateral region of femoral neck. Recent studies exploring regional adaptation of the femoral neck to physical activity have

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Compliance with Ethical Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

William Thompson, Julio Carballido-Gamio, Mariana Kersh, and Robyn Fuchs declare no conflict of interest.
Joyce Keyak declares a patent issued (#9245069).

identified heterogeneous adaptation, with adaptation principally occurring within inferomedial weight bearing regions and little to no adaptation occurring in the superolateral femoral neck.

Summary—There is a need to develop novel physical activities that better target and strengthen the superolateral femoral neck within the proximal femur. Design of these activities may be guided by subject-specific musculoskeletal modeling and finite element modeling approaches.

Keywords

bone density; bone mass; bone structure; exercise; femoral neck; osteoporosis

Introduction

Low bone mass and low-trauma (i.e. osteoporotic) fractures during aging remain a cause for concern. Over 50% of the U.S. adult population aged 50 years and older had low bone mass at either the lumbar spine or femoral neck in 2010 [1] and there were an estimated 2 million osteoporosis-related fractures in the U.S. in 2005 [2]. These values are expected to increase as a result of progressive aging of the population, with the number of osteoporosis-related fractures in the U.S. forecasted to exceed 3 million per year by 2025 [2].

Hip fractures represent a minority (<20%) of osteoporotic fractures, but are the most devastating in terms of morbidity and mortality [3]. More than half of individuals who sustain a hip fracture do not regain mobility within the first year following fracture [4], and 1-in-5 women and 1-in-3 men die during the same period as a consequence of complications [5]. Some osteoporotic hip fractures can be prevented using pharmacological approaches, with various anti-catabolic and anabolic agents shown to improve bone mass and reduce osteoporotic hip fracture risk [6, 7]. However, pharmacological approaches are typically limited to older individuals who are already at moderate-to-high risk of fracture [8]. There continues to be a need to explore non-pharmacological interventions as preventative approaches for optimizing and maintaining hip bone health prior to the increase in osteoporotic fracture risk associated with aging.

Mechanical loading associated with physical activity (of which exercise is a subcategory) has long been proposed as a means of optimizing hip bone health. The skeleton is inherently mechanosensitive, and responds and adapts to its prevailing mechanical environment [9, 10]. The extreme osteogenic potential of physical activity was recently demonstrated in professional baseball players, who exhibited a near doubling of the estimated strength of the humeral diaphysis in their throwing arm as a result of chronic exposure to repetitive, high-magnitude loading [11••]. Although the magnitude of mechanoadaptation observed in the upper extremity of baseball players is not likely achievable within the general population, it highlights the potential skeletal benefits of physical activity when loading conditions are favorable.

A relatively large body of evidence, including data from randomized controlled trials, has convincingly demonstrated the benefit of weight-bearing physical activity on hip bone health. Physical activity during growth enhances bone mineral accrual and induces geometric adaptation at the femoral neck [12–14], whereas physical activity during aging appears to primarily reduce subperiosteal bone loss to preserve proximal femoral bone mass [15, 16]. The question remains as to whether the observed benefits of physical activity on proximal femoral bone health reduce fracture risk.

The execution of a randomized controlled study to establish a reduction in proximal femur fracture risk due to physical activity-induced bone adaptation appears unachievable and, thus other levels on the research evidence hierarchy need to be considered. In order to maximize any hip fracture protective benefits of physical activity, a starting point may be to demonstrate that physical activity targets and strengthens fracture prone regions within the proximal femur.

The current paper discusses the fracture prone regions within the proximal femur, the spatial heterogeneity in proximal femur adaptation to physical activity, and how musculoskeletal modeling approaches may be used to prescribe activities that better strengthen fracture prone regions within the proximal femur.

Fracture prone regions within the proximal femur

Any region of the proximal femur can fracture under the right loading conditions; however, fractures of the femoral neck are of most concern. Femoral neck fractures account for approximately half of all proximal femur fractures [17] and are concerning because of their potential to disrupt blood flow to the femoral head which heightens risk for complications (such as non-union and avascular necrosis).

The femoral neck has a highly heterogeneous structure whose design is thought to reflect adaptation to stereotypical locomotor-related forces [18]. Models have revealed that forces during the single leg stance phase of normal walking induce maximum compressive stresses and strains inferomedially and smaller tensile stresses and strains superolaterally (Fig. 1A) [19–23]. To accommodate the habitual asymmetrical loading, the femoral neck possesses an inferomedial cortex that is much thicker than its superolateral cortex, and an associated trabecular network positioned to resist and transmit weight-bearing directed loads. The structural design provides the proximal femur with a safety factor (i.e. ratio between the maximum load that can be supported and usual loads) of approximately 5 during weight-bearing activities (i.e. level walking and stair climbing) [25]. This safety factor is relatively preserved during aging [25] as a result of preservation of inferomedial femoral neck cortical and trabecular structures [26–30].

The proximal femur is well-adapted to withstand loads in the habitual weight-bearing direction and, thus, spontaneous fractures during gait or stance are rare even during aging. In contrast, femoral neck fractures in the elderly typically occur as a result of falls with impact on the greater trochanter and in a direction broadly classified as “sideways” [31]. The proximal femur is 3–5 times more likely to fracture during a sideways fall compared to falls categorized as forward, backward or straight down, and over 30-times more likely to fracture if the sideways fall impacts the greater trochanter [32–35]. Even within the category of sideways falls, the risk of fracture varies with the precise fall direction because both the applied force and the force to fracture the proximal femur depend on fall direction [23, 36–38].

The sensitivity of fracture force to force direction is a reflection of proximal femur anatomy, with cadaveric studies demonstrating that the proximal femur can withstand forces two-to-four times greater in the single-limb stance direction than forces in a posterolateral fall direction [39, 40]. During a sideways fall onto the greater trochanter, the stress pattern within the femoral neck is reversed from that experienced during weight-bearing. Greatest compressive stresses and strains now occur in or about the region of the thin superolateral femoral neck while the thick inferomedial femoral neck is exposed to lower tensile stresses and strains (Fig. 1B) [20, 21, 23, 24, 41]. The net result is the exposure of the superolateral cortex and bone nearby to potentially injurious stress and strain, with high-speed video recordings revealing that fracture initiation during an *in vitro* simulated side-ways fall occurs within the superolateral cortex [42, 43].

In contrast to the relative maintenance of inferomedial loading-bearing structures within the femoral neck during aging, there is sharp and progressive thinning of the superolateral cortex [26, 27, 29, 30]. Clinical studies have confirmed that low cortical and trabecular bone mass and density within the superolateral femoral neck and a thinner superolateral cortex are associated with femoral neck hip fracture [26, 44].

Spatial heterogeneity of proximal femur responses to physical activity

The heightened susceptibility of the superolateral femoral neck to fracture during a sideways fall makes this a principal region of interest with regards to fracture prevention strategies. As such, it begs the question of whether the osteogenic benefits of physical activity on the proximal femur occur within the superolateral femoral neck.

Physical activity introduces a highly site-specific mechanical stimulus that induces adaptation in specific sub-volumes of bone where mechanical demands are greatest. The net result is the generation of large increases in bone strength via the addition of small amounts of mass [45, 46], which has the evolutionary advantage of creating the strong, yet lightweight skeleton required by humans for endurance tasks [47]. Previous work has demonstrated the benefits of physical activity on proximal femur bone mass, with some studies using hip structural analysis (HSA) techniques to also suggest structural adaptation [48, 49]. However, the work is limited in assessing whether physical activity adapts the superolateral cortex of the femoral neck as it used dual-energy x-ray absorptiometry (DXA) as the primary outcome.

DXA remains the clinical standard for assessing bone health, but has limitations in assessing mechanical loading-induced bone adaptation associated with physical activity as it uses a projectional radiological technique that averages large volumes of bone over a projected area [50]. The consequence can be the generation of bone size-related artifacts which have the potential to obscure important spatially heterogeneous adaptations to physical activity. The later limitation was recently highlighted in studies exploring the lasting skeletal benefits of physical activity [11••, 51–53]. Physical activity completed when young had lifelong benefits on bone size and strength, but not mass. DXA was unable to reveal this important observation as a bigger bone for the same mass provides a lower projected (areal) bone mineral density.

The HSA technique has provided a means of obtaining bone structural outcomes from DXA data. It uses the DXA bone mass image and employs the principle that a line of pixel values across the bone axis corresponds to a cut plane traversing the bone at that location. The approach provides useful additional information obtainable from DXA assessments; however, the structural outcomes remain hampered by the projectional nature of DXA. In order to estimate cortical dimensions, the HSA approach assumes cortical bone accounts for 60% of bone mass at the femoral neck and that the femoral neck is a circle with uniform cortical thickness [54]. These assumptions misrepresent the irregular cylinder structure of the femoral neck and the non-normal disruption of its cortical thickness. Cortical thickness within the femoral neck is heavily skewed toward smaller thicknesses such that mean cortical thickness overestimates thickness in 81% of regions along the femoral neck [41]. Also, the HSA approach does not allow any site-specific effects of physical activity to be established at the superolateral femoral neck.

To address the limitations of two-dimensional DXA in assessing regional benefits of physical activity within the proximal femur, preliminary work has begun to use three-dimensional (3D) imaging approaches. Nikander and colleagues [55] used magnetic resonance (MR) imaging of the femoral neck to evaluate the impact of physical activity on 3D cortical bone geometry. MR has the advantage over radiological techniques of not using ionizing radiation, but is limited by longer acquisition times potentiating motion artifacts, the non-assessment of mineral properties, and bone appearing with background signal intensity that can offer reduced contrast with surrounding connective tissues. Using a cross-sectional study design, Nikander and colleagues [55] observed young (mean age = 24.7 ± 3.8 years) female athletes competing in high impact (triple or high jump) or odd impact (soccer or squash) sports had approximately 15–30% greater mean cortical area at the femoral neck than a non-competitive, habitually active control group [55]. However, there were no group differences for cortical thickness within the critical superolateral cortex, with the greater mean cortical area in the athlete groups resulting from greater cortical thickness within the anterior, posterior and inferomedial regions of the femoral neck [55].

Abe and colleagues [56•] subsequently applied a finite element (FE) modeling approach to the MR images from the same set of subjects to predict the performance of the proximal femur during a simulated sideways fall. Athletes competing in odd impact sports had reduced von Mises stresses within 7-out-of-8 octants at the mid-femoral neck during the simulated fall. Importantly, reduced stresses were modeled within the superoanterior, superior and superoposterior octants (Fig. 2). Athletes competing in high impact sports had reduced von Mises stresses within 6-out-of-8 octants of the mid-femoral neck, but these did not include the superior and superoanterior octants.

The cumulative observations from Nikander and colleagues [55] and Abe and colleagues [56•] suggest that athletes participating in high and odd impact athletic endeavors have cortical bone adaptation principally within habitual weight-bearing regions, with some signs of adaptation in the superolateral femoral neck which may provide fracture resistance during a sideways fall. However, evaluating stress alone is insufficient for determining whether fracture resistance is improved. Reductions in von Mises stress in vulnerable regions can occur if the density and, therefore, elastic modulus and local material strength, decrease, which would instead decrease resistance to fracture. Changes in bone density and geometry can also change the fracture location which would make changes in von Mises stress at the original fracture location irrelevant. For these reasons, a valid failure theory should be implemented in this type of structural analysis to compare the local stress-strain state at each point in the bone with the local bone material properties (e.g. yield strength or yield strain) to determine whether failure will occur locally. Unfortunately, MR imaging does not provide assessment of mineral properties necessitating FE models using MR data to make a number of assumptions regarding bone apparent density which may or may not be accurate. Additional assumptions would be required to apply a failure theory and to estimate additional material properties. Also, the cross-sectional study design wherein proximal femur bone properties were compared between different individuals does not adequately control for selection bias. It is possible that the enhanced proximal femur properties in the athlete groups resulted from influences beyond loading history, such as genetic and other environmental factors.

Two groups have longitudinally mapped proximal femur adaptation to physical activity by applying ‘computational anatomy’ approaches to computed tomography acquired data [57••, 58•]. Computational anatomy is a set of imaging analysis techniques that model anatomical structures in images as curves, surfaces, maps, and volumes with the objective of combining them across subjects to create statistical feature maps [59]. The approach has the potential to identify sub-volumes of tissue at the resolution of a few millimeters impacted by physical activity, and encompasses techniques known as voxel-based morphometry (VBM) for mapping 3D density values, tensor-based morphometry (TBM) for mapping regional shape differences, and cortical bone mapping (CBM) for mapping 3D cortical density, mass and thickness.

Lang et al. [58•] used VBM and CT scan-based FE models to longitudinally explore adaptation within the proximal femur to two different lower-body resistance training regimes. Healthy, adult participants completed a 16-week resistance exercise program consisting of either open-kinetic chain hip abduction and adduction exercises or closed-kinetic chain (i.e. weight bearing) squats and deadlifts, or a combination of both. The general hypothesis was that hip abduction/adduction exercises would have a spatially distinct and larger osteogenic effect than squats/deadlifts as the forces during abduction/adduction were predicted to be in a direction that occurred along axes in which the hip is not typically loaded. This hypothesis is somewhat simplistic considering the hip abductors are important during the single-leg stance phase of gait and, thus the proximal femur is habitually exposed to hip abductor forces.

Nevertheless, there were some spatial differences in regional adaptation between the exercise groups, with the abduction/adduction and squats/deadlifts exercise groups showing changes primarily in the regions of the greater trochanter and inferomedial femoral neck, respectively (Fig. 3), causing FE-computed fracture load in single-leg stance loading to increase by 9% in the squats/deadlifts group, but no change in the abduction/adduction group. Neither exercise group appeared to exhibit adaptation in the fracture critical superolateral femoral neck, which is consistent with the lack of change in FE-computed fracture load in both groups during loading simulating a fall onto the greater trochanter. Also of note is the short duration of the exercise intervention performed in a heterogeneous small sample (7–8 participants per group containing a mix of males and females aged 25–55 years), which may have influenced power to detect group differences in the fracture relevant superolateral femoral neck.

The latest study to use a 3D imaging approach to explore adaptation of the proximal femur to physical activity was performed by Allison and colleagues [57••, 60]. Performing a randomized, within-subject controlled study, they had 32 older men (mean age = 69.9 ± 4.0 years) complete a 12 month high-impact unilateral exercise intervention which increased to 50 multidirectional hops, 7 days a week on one randomly allocated leg. The contralateral leg served as an internal control site and was not exercised. Using CBM to regionally map adaptation, increases in cortical mass surface density and endocortical trabecular density were observed in the inferoanterior femoral neck and greater trochanter, with some adaptation also observed in the superolateral femoral neck (Fig. 4) [57••]. These data suggest that hopping-type physical activities may have some benefit on the superolateral femoral neck; however, changes in regional bone properties over time in the exercised leg were not statistically compared to changes over time in the contralateral control leg. As a consequence, it remains unclear whether the exercise intervention significantly induced changes beyond normal maturation over time. Also, the study was unable to identify any regional differences in proximal femur cortical thickness or cortical density.

Designing better activities for strengthening fracture prone regions within the proximal femur

The few studies exploring regional adaptation of the proximal femur to physical activity have been heterogeneous in terms of subjects investigated, physical activities performed and methodology used to localize adaptation. However, the cumulative findings suggest that adaptation was primarily induced in inferomedial femoral neck regions and muscle insertion sites of the greater trochanter, with little to no adaptation in fracture-relevant superolateral femoral neck regions.

The patterns of adaptation induced in the previous studies are not overly surprising considering the physical activity modes studied generally loaded the proximal femur in habitual loading directions. Lang et al. [58•] and Sievänen and colleagues [55, 56•] endeavored to explore adaptation to less habitual loading; however, based on the limited adaptation observed at the superolateral femoral neck and aforementioned limitations associated with each study, it remains unclear whether the physical activity modes were able to impact fracture risk during a fall onto the greater trochanter. In particular, Lang et al. [58•] was unable to demonstrate a benefit of physical activity on estimated strength of the proximal femur during a posterolateral fall using a validated FE model. Based on the relative null findings of the preliminary studies exploring regional adaptation of the proximal femur to physical activity, there appears a need to design novel activities that load the proximal femur in non-habitual directions so as to induce adaptation in the vicinity of the superolateral, anterior and posterior femoral neck.

The ability of different tasks to load fracture prone regions of the femoral neck may be revealed by mapping the distribution of stresses and strains within the proximal femur. As invasive measurement of stress and strain distributions within the femoral neck is not an option, non-invasive methods are required. Computational modeling is the most viable method for estimating stress and strain fields within the proximal femur as it is non-invasive and potentially enables subject-specific identification of physical activities to enhance stress/strain in specific regions of the femoral neck. The subject-specific nature of the modeling potentially enables a precision medicine approach for the prescription of physical activities to strengthen the femoral neck of individual patients.

Computational modeling involves the use of mathematics, physics and computer science to simulate complex systems. With regards to the proximal femur, the most extensive use of computational modeling has been in the form of FE models based on computed tomography scans to obtain subject-specific estimates of femoral neck strain [61, 62] and fracture load [63–70] during simulated tasks. The FE models have been informative in terms of illustrating loading of the proximal femur to a set of loading conditions; however, they have possessed the limitation of not taking into account subject-specific muscle and joint function features.

Musculoskeletal models are an idealized mathematical representation of the body, and have recently been developed to calculate subject-specific loading of the proximal femur [71–73]. The models involve: 1) taking accurate measures of the forces being applied to the body, typically via the measurement of ground reaction forces using force platforms; 2) taking accurate measurements of body-segmental motion, typically obtained using video-based motion capture techniques, and; 3) having an accurate knowledge of muscle and joint contact loading [72]. The latter involves using a combination of data from *in vivo* studies, such as electromyography to establish muscle activity patterns during an activity and imaging to calculate muscle size and structure, and *ex vivo* studies, such as cadaver dissections to determine musculotendinous mechanical properties and muscle insertions and angles of pull.

Subject-specific force, motion and musculoskeletal anatomy data can be combined in a musculoskeletal model to predict forces acting about the hip of an individual during different physical activities (Fig. 5A). These predicted muscle and joint forces can then be applied to an FE model of the proximal femur developed from CT imaging data of that individual to map the distribution of stresses and strains at the femoral neck in a subject-specific and physical activity-specific manner (Fig. 5B). Via this approach, it is possible to develop an individualized or personalized medicine approach to physical activity prescription for strengthening the proximal femur.

Martelli and colleagues [74] performed the first and, to date, only quantitative assessment of femoral neck loading during differing activities using computational methods. Using a lower-limb musculoskeletal model, they reported on the distribution of strain energy and peak tensile strain within the femoral neck during 15 different activities in a single individual. Data suggested that one-legged long jump and maximum isokinetic hip extension induced the highest changes in strain energy, while maximal hip extension and knee flexion exercises maximally loaded the thinnest region of the superolateral femoral neck. Also of note, they observed that activities of relatively similar ground reaction forces were capable of producing contrasting levels and distributions of femoral neck strain and strain energy [74]. The latter observation was likely due to the recruitment of different muscles with different geometric arrangements, and suggests that the measurement of ground reaction forces to design and prescribe proximal femur loading programs may be imprecise.

The data reported by Mantelli and colleagues [74] are limited with regards to the study of a single individual and the application of musculoskeletal loads calculated from a young volunteer to an FE model of the proximal femur from an older individual. However, the contribution highlights the potential of computational musculoskeletal modeling in designing activities that may better strengthen fracture prone regions within the femoral neck. Moving forward, there is a need to model femoral neck loading in a broader population to better identify specific activities that load the proximal femur in non-habitual directions so as to optimize adaptation of the fracture relevant superolateral femoral neck.

Conclusions

By combining musculoskeletal modeling approaches with 3D imaging techniques it may be possible to design and assess the benefits of specific physical activities targeting fracture prone regions within the proximal femur, such as the superolateral femoral neck. Whether regionally-observed changes in proximal femur bone mass and/or morphometry correspond with a reduction in osteoporotic fracture risk will remain open to debate without supportive evidence from controlled trials. Also, the techniques involved remain in their infancy and are associated with limitations, including radiation concerns associated with imaging for FE model development and partial volume effects due to a trade-off between radiation dose and image resolution. Despite these concerns, the assessment of the regional skeletal benefits of physical activities designed with the assistance of subject-specific musculoskeletal modeling opens the potential for a personalized medicine approach to the prescription of activities that better strengthen fracture prone regions within the proximal femur.

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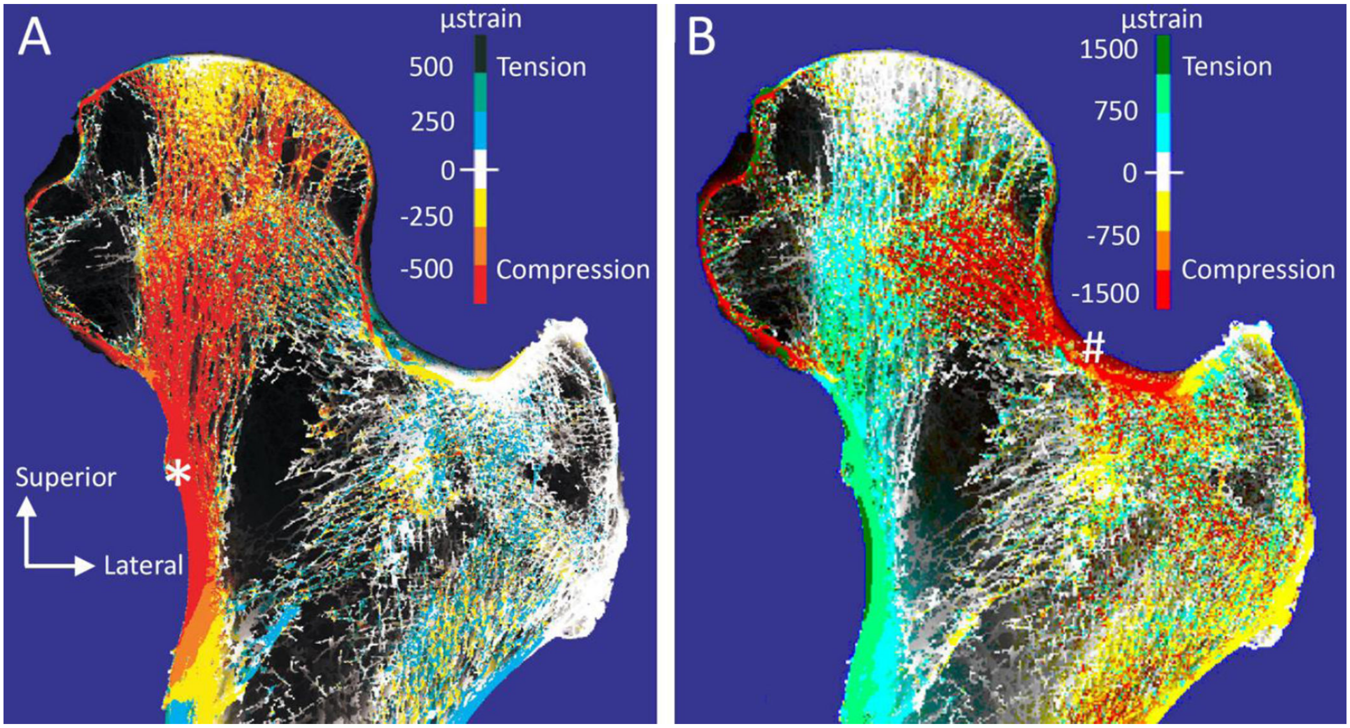

Figure 1.

Distribution of strain within an osteoporotic proximal femur during: A) the stance-phase of normal walking and B) a simulated sideways fall onto the greater trochanter. Maximum compressive strains are modelled to occur inferomedially (*) and smaller tensile strains superolaterally during walking. The strain distribution pattern is reversed during a sideways fall, with maximum compressive strains now occurring in the thin superolateral femoral neck (#) while the thick inferomedial femoral neck is exposed to lower tensile strains. Panel A reproduced from Van Rietbergen et al. [22] with permission from John Wiley & Sons, Inc. Panel B reproduced from Verhulp et al. [24] with permission from Elsevier.

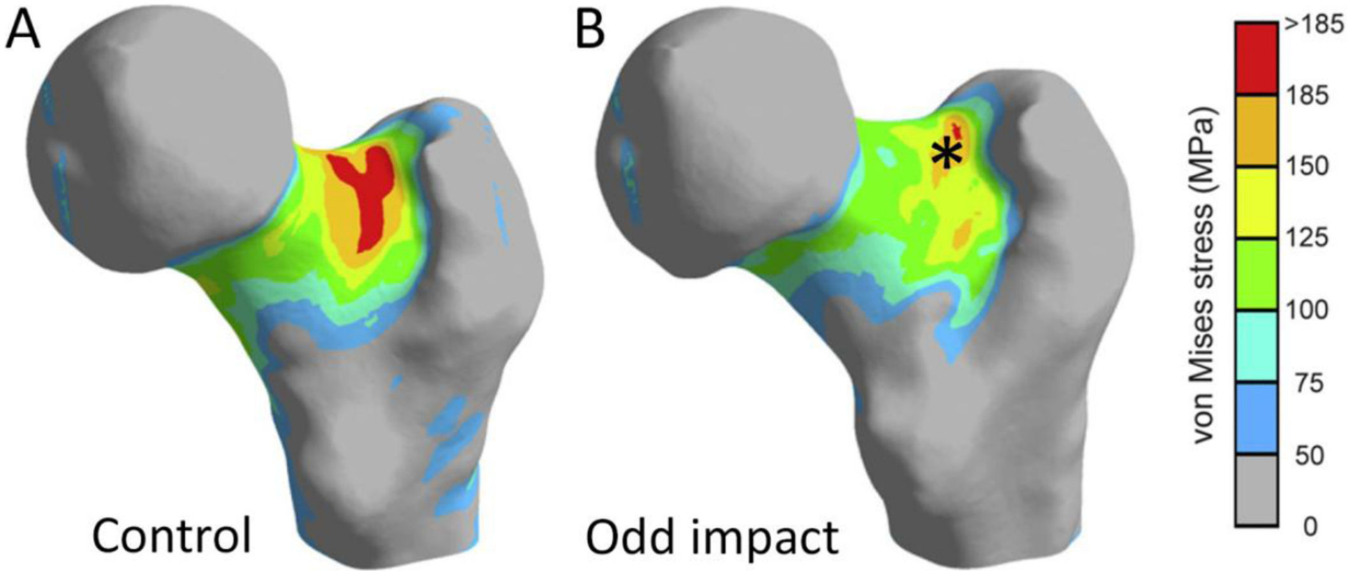

Figure 2.

Posterior views of the proximal femur showing example typical von Mises stress distributions in the: A) control and B) odd impact sports groups. Note the reduced stresses in the superoposterior region of the odd impact sports group (*). Reproduced from Abe et al. [56] with permission from Elsevier.

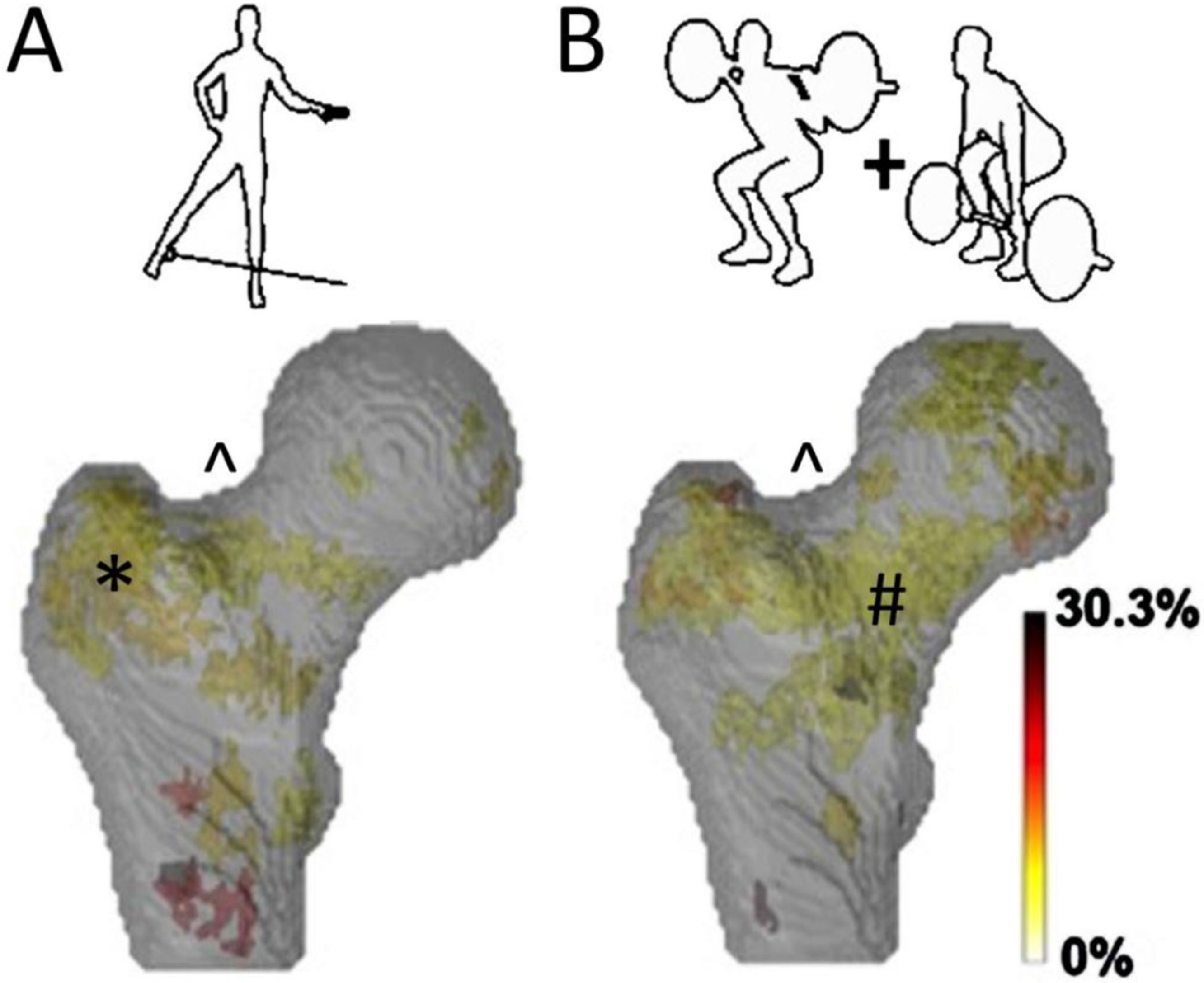

Figure 3.

Clusters of voxels identified as being significantly different following 16 weeks of: A) hip abduction and adduction strengthening exercises and B) squat and deadlift exercises. The abduction/adduction and squats/deadlifts exercise group showed changes primarily in the regions of the greater trochanter (*) and inferomedial femoral neck (#), respectively. Neither group appeared to exhibit adaptation at the superolateral femoral neck (^). Reproduced from Lang et al [58] with permission from John Wiley & Sons, Inc.

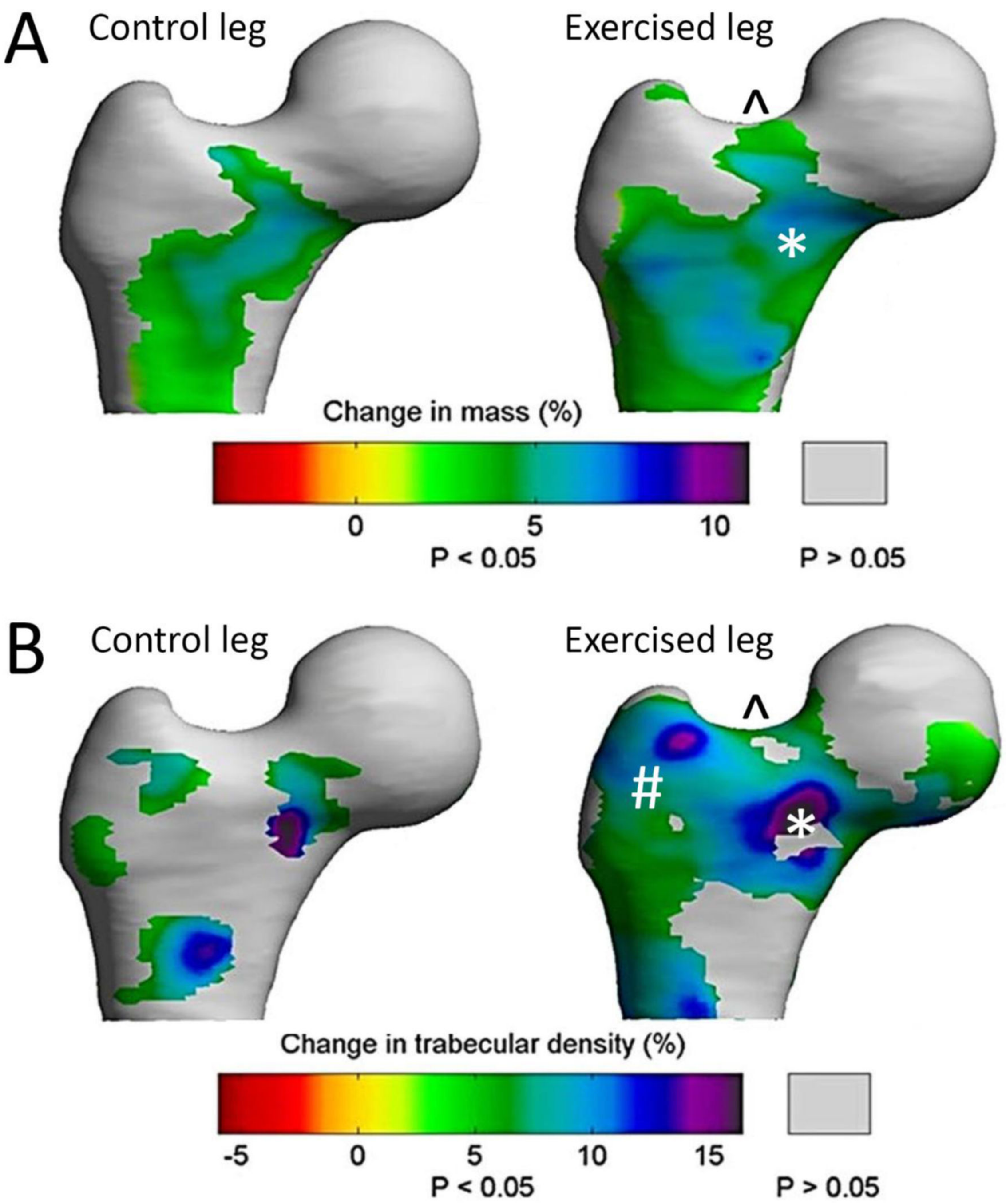

Figure 4.

Anterior views of the percentage change in: (A) cortical surface mass density and (B) endocortical trabecular density in the control and exercise legs following 12 months of unilateral hopping exercise. The exercise leg appeared to have larger regions of cortical surface mass (*) and endocortical trabecular (#) density change in the inferomedial femoral neck than observed in the control leg, with the region of endocortical trabecular density change in the greater trochanter also appearing larger than in the control leg. There was some extension of the region change towards of the superolateral femoral neck within the exercised leg (^). Reproduced from Allison et al [57] with permission from John Wiley & Sons, Inc.

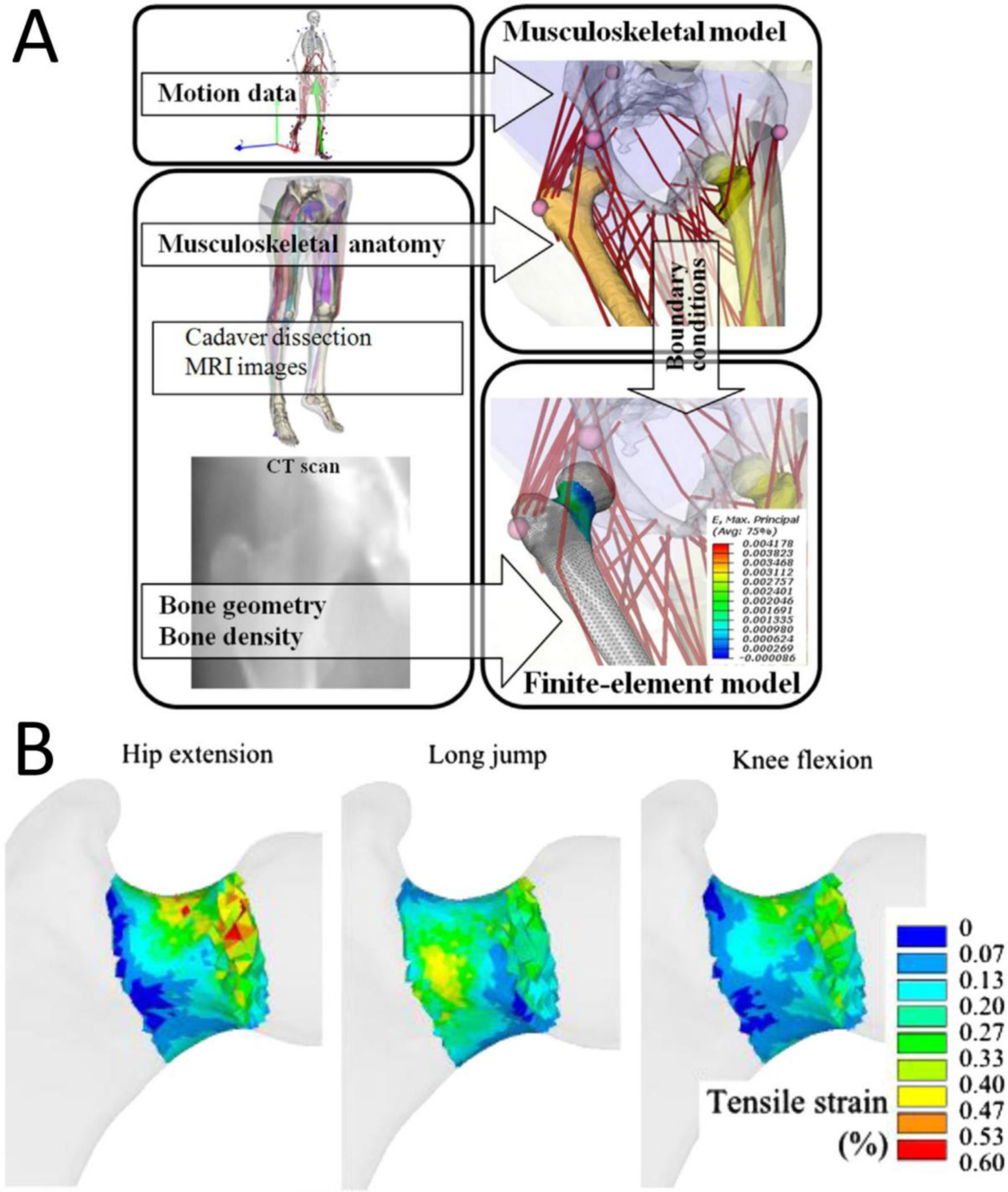

Figure 5.

(A) Overview of the integrated musculoskeletal and finite-element modeling process used to determine subject-specific stresses and strains at the femoral neck. (B) Distribution of tensile strain within the femoral neck during hip extension, long jump and knee flexion exercises. Reproduced from Martinelli et al [74] with permission from Elsevier.